Investigating CRV431 in NASH Patients: Data From the Phase 2a AMBITION Study

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DIGITAL EXPERIENCE

INTRODUCTION

Nonalcoholic Steatohepatitis (NASH): Global prevalence increasing worldwide with significant morbidity and mortality and no approved pharmacotherapy

CRV431 is a clinical phase drug candidate that inhibits cyclophilin isomerases and attenuates hepatic fibrosis in multiple NASH rodent models.

AIM

- To assess the safety, tolerability, and pharmacokinetics (PK) of CRV431 in subjects with presumed NASH fibrosis stage 2 or 3 (primary endpoints)
- Exploratory endpoints evaluated NASH biomarkers (transaminases, Enhanced Liver Fibrosis (ELF)-score, Pro-C3, Fibroscan, collagens, matrix metalloproteinases, whole blood transcriptome, and serum lipidome)

MATERIAL & METHODS

Phase 2a single-blind, placebo-controlled trial (NCT04480710) was conducted at 10 research sites (USA) in 43 subjects.

Fig 1: AMBITION: A Phase 2a, **M**ulti-center, Single-**B**lind, Placebo-Controlled, Proof of Concept Study to Evaluate the Safety & **T**olerability of CRV431 Dosed **O**nce Daily in **N**ASH Induced F2 & F3 Subjects

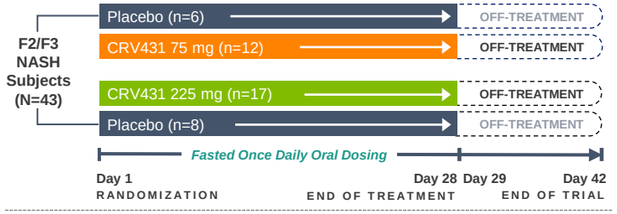


Fig 2: Baseline demographics

		CRV431 75 mg (n=12)	CRV431 225 mg (n=17)[a]	Pooled Placebo (n=14)
Age (years)	Mean (SD)	61.9 (8.0)	54.0 (13.3)	61.1 (12.0)
Gender	Male n (%)	7 (58.3)	7 (41.2)	9 (64.3)
Race	White n (%)	11 (91.7)	17 (100)	13 (92.9)
	Hispanic n (%)	1 (8.3)	1 (7.1)	2 (4.7)
BMI (kg/m^2)	Mean (SD)	35.0 (8.0)	37.7 (6.4)	38.9 (8.8)
ProC3 (ng/mL)	Mean (SD)	23.8 (8.2)	23.6 (20.0)	22.1 (8.1)
ALT (IU/mL)	Mean (SD)	60.5 (39.1)	36.1 (15.7)	60.8 (33.0)

[a]1 subject with active COVID.

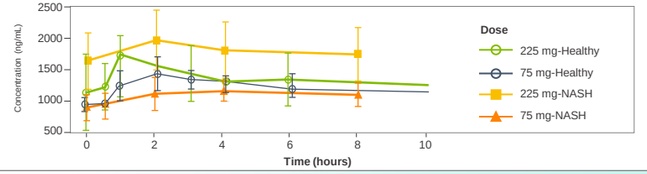
RESULTS

Primary Endpoints

Fig 3: Adverse events related to study drug

- All events we categorized as not serious
- Mild AEs include constipation at 75 and 225 mg
- There were 2 patients with mild diarrhea
- 225 mg: 1 report of fatigue, lips tingling, constipation, increased weight, headache, and diarrhea

Fig 4: Day 28 whole blood concentration of CRV431 by dose and health status (Mean ± 95% CI)



Exploratory Endpoints

Fig 5: ALT change from baseline (Mean ± 95% CI)

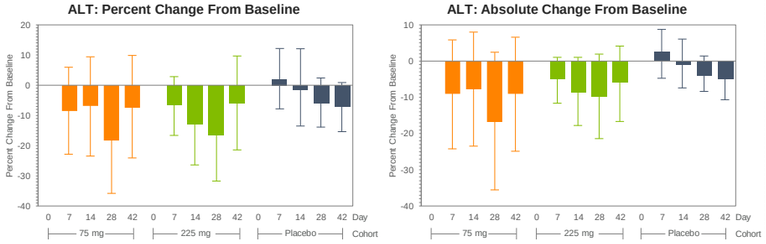


Fig 6: Change from baseline in released N-terminal pro-peptide of type III collagen (Mean ± 95% CI) (Pro-C3 for baseline >17.5 ng/mL)

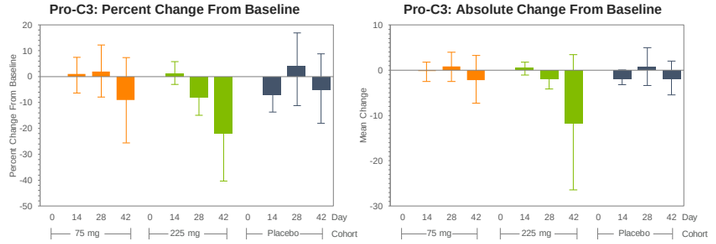


Fig 7: PK-PD of modeling of CRV431 concentration predicts ALT and Pro-C3

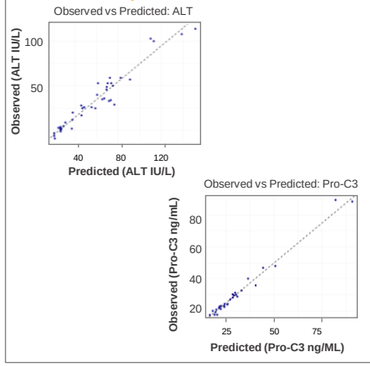
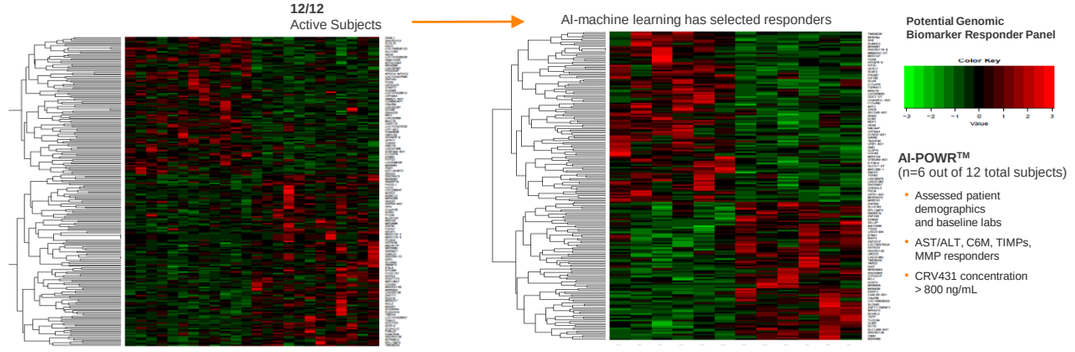


Fig 8: Standard differentially expressed genes – DESEq2



CONCLUSION

- 28 days of CRV431 dosing at 75 mg or 225 mg was safe and well tolerated
- PK of CRV431 was linear and similar to healthy subjects
- ALT decreased in 50%, 67%, and 87% of the subjects in the placebo, 75 mg, and 225 mg cohorts, respectively
- There was a reduction from baseline for the 225 mg cohort that had baseline Pro-C3 >17.5 ng/mL. This indicates a reduction in fibrosis for patients with active fibrosis at baseline. Reductions correlate with ALT changes
- PK-PD of modeling of CRV-431 concentration accurately predicts ALT and Pro-C3
- Transcriptomics and artificial intelligence (AI) identifies responders based on DESEq2. AI training can decrease heterogeneity and predict a priori who will respond to CRV431 based on standard differentially expressed genes

CONTACT INFORMATION

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